REMARKS

As discussed during the interview which took place December 10, 2009, this amendment seeks to simplify the issues and to place at least some of the subject matter described in the application in immediate condition for allowance. The applicant reserves the right to pursue additional claims which are adequately described in the application and drawings in one or more continuing applications.

In particular, all of the claims now presented require

(1) a reversed cubic phase material (as noted during the interview and in prior correspondence with the Examiner, reversed cubic phases are of particular interest to the applicant, and are physically distinct from other types of fluids and mixtures)

(2) the reversed cubic phase material being from

a) water,

b) phospholipids,

c) an essential oil or a component thereof or tocopherol, and

d) a difficult to solubilize pharmaceutical active solubilized in or solubilizable in the reverse cubic phase material.

As noted during the interview, and as will be discussed in more detail below,

when tocopherol or an essential oil (or a component thereof) is NOT present, one ordinarily does NOT obtain a reversed cubic phase structured fluid from water, phospholipids, and a difficult to solubilize pharmaceutical active, and

when tocopherol or an essential oil is present one is able to solubilize significantly more of a difficult to solubilize drug in a reversed cubic phase structure fluid that includes water, phospholipids and the difficult to solubilize pharmaceutical active than if the tocopherol or essential oil were not present.

Further, as will be discussed in more detail below, and in the accompanying declaration of Dr. David Anderson, the prior art references (1) do not show a reversed cubic phase material formed from water, phospholipids, an essential oil or component thereof or tocopherol, and a difficult to solubilize pharmaceutical active, and (2) do not show or suggest the use of an

essential oil or a component thereof or tocopherol as a solubilizing agent to solubilize difficult to solubilize pharmaceutical actives into reverse cubic phase materials.

This response seeks to address issues raised in the office action as well as the Examiner's Interview. The concurrently filed declaration clarifies matters pertaining to the inventor's prior patent application (the "Anderson" reference). In addition, for ease of review, a table identifying support for the claimed subject matter is attached hereto.

Claims 66-68 and 70-111 are currently pending in the application. By this amendment, claims 66-68 are amended, claims 1, 3-27, 29-53, 56, 59-60 and 69 are canceled and new claims 70-111 are added for the Examiner's consideration. The foregoing separate sheets marked as "Listing of Claims" show all the claims in the application, with an indication of the current status of each.

Cancellation of claims herein is without prejudice or disclaimer and is intended to accelerate prosecution of the application by simplifying outstanding issues. The Applicant reserves the right to pursue the subject matter of he cancelled claims, or claims to other disclosed subject matter, in one or more continuation applications.

Claim Objections

Claim 9 is objected to due to the recitation of "I" instead of "1". Claim 9 is hereby canceled, thereby making moot this objection.

Claim Rejections: 35 USC § 112

First paragraph

Claims 1, 3-14, 52 and 60 stand rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. Claims 1, 3-14, 52 and 60 are hereby canceled, thereby making moot this rejection.

Second paragraph

Claims 10, 22-26 and 47-51 stand rejected under 35 USC § 112, second paragraph, due to purported indefiniteness. Claims 10, 22-26 and 47-51 are hereby canceled, thereby making moot this rejection.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim Rejections: 35 USC § 103(a)

In order to simplify outstanding issues and to accelerate prosecution, claims 1, 3-27, 29-53, 56, 59-60 and 69 are hereby cancelled. Cancellation of these claims makes a number of the Examiner's 103(a) grounds of rejection moot. For convenience, Applicant's responses to these now entirely moot rejections are not presented herein in the order in which they appeared in the Office Action, but are grouped below under the subheading "103(a) Rejections that are Moot in Entirety". Applicant's response to the two 103(a) rejections that remain in part are presented beginning after the subheading "103(a) Rejections that Remain in Part".

103(a) Rejections that are Moot in Entirety:

Claims 16 and 41 stand rejected under 35 USC § 103(a) as obvious over Anderson (supra) in view of Unger et al, (US patent 6,090800, hereinafter "Unger"). Claims 16 and 41 are hereby canceled, thereby making moot this rejection.

Claims 20 and 45 stand rejected under 35 USC § 103(a) as obvious over Anderson (supra) in view of Wehling et al, (US patent 5,223,264, hereinafter "Wehling"). Claims 20 and 45 are hereby canceled, thereby making moot this rejection.

Claims 25-26 and 50-51 stand rejected under 35 USC § 103(a) as obvious over Anderson (supra) in view of Yamakawa et al, (JP 08143475, hereinafter "Yamakawa"). Claims 25-26 and 50-51 are hereby canceled, thereby making moot this rejection.

Claims 17, 25-26, 42 and 50-51 stand rejected under 35 USC § 103(a) as obvious over Engstrom (supra) in view of Yamakawa (supra). Claims 17, 25-26, 42 and 50-51 are hereby canceled, thereby making moot this rejection.

103(a) Rejections that Remain in Part

Anderson

Claims 1, 3-15, 17-19, 21-24, 27, 29-40, 42-44, 46-49, 52-53, 56, 59-60 and 66-69 stand rejected under 35 USC § 103(a) as obvious over Anderson (WO9912640; page 8 of Office Action). This rejection is traversed. Claims 1, 3-15, 17-19, 21-24, 27, 29-40, 42-44, 46-49, 52-53, 56, 59-60 and 69 are hereby canceled, thereby making moot this portion of the rejection. Only the rejection of claims 66-68 remains.

The present invention is directed to solubilizing difficulty soluble pharmaceutical actives so that they may be used in drug delivery. Specifically, the invention embodies the discovery that difficultly soluble pharmaceutical actives, defined as less than about 5% by weight soluble

in soybean oil, can be solubilized in a reversed cubic liquid crystalline phase structured fluid of a defined composition. The reversed cubic phase material must contain: (i) water; (ii) a phospholipid; and (iii) an essential oil (or component thereof) or tocopherol, or a mixture thereof. Compositions with these components as taught in the present invention surprisingly form reversed cubic liquid crystalline phase structured fluids (with their unique and highly useful properties) and surprisingly and unpredictably can incorporate relatively high concentrations of these otherwise difficult to solubilize pharmaceutical actives. The presence of the essential oil or tocopherol in the water / phospholipid composition is necessary for 1) formation of a reversed cubic phase structured fluid and 2) a high level of solubilization of the pharmaceutical active in said reversed cubic phase structured fluid. Thus, when the essential oil or tocopherol is absent from said composition, 1) the resulting composition is typically *not* a reversed cubic phase structured fluid, and 2) the concentration of pharmaceutical active in the structured fluid that can be achieved is significantly less than the concentration which is solubilized in the composition in which the essential oil/tocopherol is present.

Feature #1 (requirement of essential oil or tocopherol for formation of reversed cubic phase) was addressed during the telephone Interview of December 10, 2009, in particular by the inventor, Dr. Anderson. As discussed during the Interview, the lack of formation of reversed cubic phase in the claimed compositions in the absence of an essential oil or tocopherol is illustrated in the three phase diagrams attached to the Declaration, which show that no cubic phase is formed from phospholipid and water (diagram 1), but that the addition of tocopherol (diagram 2) or essential oil of spearmint (diagram 3, originally presented in a Declaration submitted with the response filed March 26, 2009), induce a phase change to a reversed cubic phase.

With respect to Feature #2 (increased loading of difficult to solubilize pharmaceutical active), this feature was also discussed during the telephone Interview. During the Interview, the Examiner inquired whether experimental evidence was available to support a contention that reversed cubic phase material as claimed herein did dissolve more of such pharmaceutical actives. Applicant referred Examiner to Exhibit 5 of the Declaration filed with the response of March 26, 2009, in which evidence was provided that the reversed cubic phases of the present invention do solubilize greater amounts of paclitaxel than do reversed cubic phase materials of other compositions, specifically those that lack either an essential oil (or component thereof) or

tocopherol. In addition, in the Declaration provided herewith, Dr. Anderson avers that this is the case.

In the Declaration filed March 26, 2009, Dr. Anderson described the two-pronged impact of tocopherol or essential oils on the morphology and composition of the lipid bilayer in the phospholipid/water system as taught in the invention. The two prongs are: (i) to cause a change in the packing of lipids in the bilayer—specifically, a "fanning out" of the fatty chains—so as to *induce a phase change* to a reversed cubic phase material; and, (ii) to enrich the bilayer with polar groups, *allowing an increase in concentration* of pharmaceutical actives which are described by the invention (less than 5% soluble by weight in soybean oil). A pharmaceutical active which has high solubility in soy oil has a relative dearth of polar groups; by contrast, a pharmaceutical active which has low solubility in soy oil has a relative abundance of polar groups. Thus it is recognized for the first time in this invention that incorporation in a lipid bilayer of a pharmaceutical active with relatively abundant polar groups is strongly promoted by the addition of the essential oil or tocopherol; and, synergistically with this, the same addition concurrently creates a reversed cubic phase with its many highly favorable drug-delivery properties.

Claims 98-100 are directed to these defined compositions. The compositions comprise a reversed cubic liquid crystalline phase comprising four components, two of which are water and phospholipid. The third component is an essential oil or component thereof (claim 98), tocopherol (claim 99), or an essential oil or component thereof, or tocopherol or a mixture thereof (claim 100). The fourth component in all cases is a pharmaceutical active which must *be* less than 5% by weight soluble in soybean oil.

In the Office Action Examiner specifically referred to, and during the Interview specifically requested clarification regarding, the teachings presented in Examples 36 and 37 of Anderson. Accordingly, Applicants note the following:

Example 36: The mixture of components taught in this Example (eugenol, soy lecithin phospholipids and glycerol) is not the same as that of the present invention. This mixture contains glycerol instead of water, and when mixed together, the components do not form reversed cubic phase material. Rather, a nanostructured liquid phase, coated with crystalline iodine, is formed. Evidence to this effect is provided in the accompanying Declaration by the inventor, Dr. Anderson. In addition, although paclitaxel is solubilized in the nanostructured

liquid phase that is formed at a level of 3%, the loading is described as "metastable" and precipitation of paclitaxel crystals occurs rapidly with time. It is suggested that precipitation might be prevented by decreasing the amount of paclitaxel to e.g. "…0.7% or less…". In contrast, as established in the accompanying Declaration and in Exhibit 5 of the Declaration filed March 26, 2009, the reversed cubic phase materials of the present invention provide much higher loadings in stable formulations from which paclitaxel does not precipitate. The levels of stable paclitaxel loading that are achieved in the practice of the present invention (e.g. when essential oils are included) is generally from at least about 3% up to nearly 4.5% (see Table and Graph referred to as Exhibit 5 in the Declaration filed March 26, 2009).

Example 37: The mixture of components taught in this Example is soy lecithin phospholipids, water and anisole. Anisole is not an essential oil or component thereof. Thus, this example does not teach the combination of components required by the claims of the present invention. Evidence that anisole is NOT an essential oil is provided herewith. Printouts of entries for "anisole" from Wikipedia (on line) and the Merck Index (hard copy, volume 12, page 113, published 1996) are provided herewith. As can be seen, all preparation methods for anisole are synthetic; no natural source is cited. Anisole is, however, described as having an odor "reminiscent of anise seed" and can be used as the basis of making synthetic forms of other compounds such as the essential oil "anethole". In contrast, printouts of entries from Wikipedia and the Merck Index (pages 108-109, attached) for an essential oil such as anethole clearly state that anethole is a "chief constituent of anise, star anise and fennel oils" (Merck Index) and that the compound "occurs widely in nature, in essential oils" (Wikipedia). Clearly, anethole is a major essential oil component, while anisole is not but is, instead, a synthetic chemical entity. Furthermore, as alluded to in the Declaration of David Anderson currently filed herewith, "metastable" means that only low levels of loading are achieved.

In summary, in spite of the extensive teachings of Anderson, there is no teaching therein which addresses the solubilization of substances that are less than 5% by weight soluble in soybean oil. Anderson does not distinguish such compounds, nor discuss or allude to these criteria, nor suggest or render obvious these criteria to one of skill in the art, let alone discuss, suggest or render obvious a solution for solubilizing such compounds in a pharmaceutically acceptable cubic phase composition. In particular, Anderson does not discuss, allude to or in any way render obvious the defined compositions recited in the present claims. Crucially, Anderson

also fails to teach that this same incorporation of essential oil/tocopherol, under conditions taught in the instant specification, induces the conversion of the lamellar phase in phospholipid – water mixtures to reversed cubic liquid crystalline phases of high utility, thus bringing highly desirable and even endogenous phospholipids into the realm of cubic phase-based drug delivery.

It is Applicant's position that the use of Anderson as an obviousness reference is not valid in view of the Federal Circuit decision *In re* Kubin [561, F.3d 1351 (Fed. Circ. 2009)], which addresses rejections based on combinations which are, according to an Examiner, allegedly "obvious" to try in view of one or more references, such as those combinations recited in the present claims. *In re* Kubin affirmed *In re* O'Farrell [853 F.2d 894, 903 (Fed. Cir. 1988)] which stated that one class of cases where "obvious to try" is erroneously applied is when "…what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result…". It is Applicants' position that Anderson is not a proper 103(a) reference because the selection of the defined components of the compositions claimed herein was made from many choices which were listed but not in any way emphasized or further characterized in Anderson. For example, the selection of phospholipid is not obvious based on Anderson. In describing the various possible components of the particle, Anderson states (column 25, lined 39-61) "Suitable surfactants or block copolymer components (or mixtures thereof) may include: a. cationic surfactant b. anionic surfactant c. semipolar surfactant c. zwitterionic surfactant i. in particular, a phospholipid ii. a lipid mixture containing phospholipids, designed to match the physico-chemical characteristics of a biomembrane d. monoglyceride e. PEGylated surfactant f. one of the above but with aromatic ring g. block copolymer i. with both blocks hydrophobic, but mutually immiscible; ii. with both blocks hydrophilic, but mutually immiscible; iii, with one block hydrophilic and the other hydrophobic, i.e., amphiphilic) h. a mixture of two or more of the above." Applicant notes that the category that includes phospholipids, zwitterionic surfactants, is only one category out of eight that are listed. The paragraph beginning at lines 62 of column 25 provides suggestions of phospholipids that may be employed, but also lists glycolipids, sphingolipids, salts of cholic acids, ad well as "gentiobiosyls, isoprenoids, ceramides, plasmologens, cerebrosides (including sulphatides), gangliosides, cyclopentatriol lipids, dimethylaminopropane lipids, and lysolecithins and other lysolipids which are derived from the above by removal of one acyl chain." In addition, Applicant notes that phospholipids are not listed in the description of "preferred

surfactants" or even as preferred zwitterions, in the paragraphs beginning at line 14 of column 26 and ending at line 36 of column 27.

The same is true for "essential oils". Examiner refers to the teaching of "natural oil extracts" (lines 60-61 of column 27). Applicant notes that this language is buried in a list of possible "Suitable third components" beginning on line 51 of column 27 and extending through line 23 of column 28, with no particular emphasis or teaching of any one substance. Vitamin E itself is only one of the long list (see last item in the list). Likewise, line 17 of column 6 states that "In terms of solvents, water is not the only polar solvent" and continues to provide a list that extends to line 36 of that column. This analysis does not even take into account that the selection of a three-component system is only one of four possibilities taught by Anderson (see column 25, lines 23-30, where a. a polar solvent and a surfactant, c. a block copolymer and d. a block copolymer and a solvent are also listed). Without providing an exact mathematical calculation of the possibilities, Applicant submits that a conservative estimate of the number of combinations taught by Anderson that one of skill in the art might try would number in the tens or perhaps hundreds of thousands. Thus, this situation falls into the category of one in which an obviousness rejection is, according to *In re* Kubin, being applied erroneously. And this is also assuming that the skilled person would somehow have first correctly conjectured that some composition of Anderson might be useful for solubilizing in cubic phase at greater loadings the precise category of difficultly soluble compounds recited in the present claims, which categories are also not taught by Anderson, or elsewhere. Indeed, only a small fraction of compositions that yield the nanostructured liquid and liquid crystalline phase materials in Anderson are reversed cubic phases, requiring even further experimentation after such a conjecture, whereas in contrast, the instant invention provides information on which lipid, which essential oils (or tocopherol), and which ratios thereof will produce a reversed cubic phase of utility. Applicant respectfully submits that deeming this scenario as "obvious" is neither reasonable nor likely. It is the present inventor who, by a combination of extensive investigation and serendipity, was able to identify the defined combinations which work for this particular purpose. However, this discovery was not in any respect obvious in view of the teachings of Anderson.

Engstrom and Unger

Claims 1, 3-16, 18, 27, 29-41, 43, 52-53, 56, 59, 66 and 68-69 stand rejected under 35 USC § 103(a) as obvious over Engstrom et al. (US patent 5,151,272, hereinafter "Engstrom") in

view of Unger (supra; page 17 of Office Action). This rejection is traversed. Claims 1, 3-16, 18, 27, 29-41, 43, 52-53, 56, 59 and 69 are hereby canceled, thereby making moot this portion of the rejection. Only the rejection of claims 66-68 remains.

Examiner admits that Engstrom does not, in and of itself, anticipate or render obvious the present Invention. Applicant concurs. Engstrom does not teach any of the compositions claimed herein. Engstrom's teaching is the formation of cubic phase materials incorporating drug using lipids alone. Every Engstrom example of a cubic phase composition uses the monoglyceride monoolein, and every Engstrom claim covering cubic phase materials requires a monoglyceride. In contrast, monoglycerides are not required in the claims of the present Application; they are not used in the examples in the specification. Monoglycerides are not acceptable for injection, and the requirement for their use severely limits the utility of Engstrom. Monoglycerides (also known as monoacylglycerols) are lipids. Engstrom makes no mention whatsoever of an approach using non-lipid co-solubilizers for forming cubic phase materials, as is the basis of the present Invention. In addition, Engstrom does not discuss or identify difficultly soluble substances, and certainly does not identify that certain subset of difficultly soluble substances which are less than 5% by weight soluble in soy oil and which are the focus of the instant Application. Nor does Engstrom teach the incorporation of difficultly soluble substances in the cubic phase materials described herein. In particular, nearly all of the drugs used in the Examples of Engstrom are known to be well-solubilized by liquid fats, and would thus be expected to be more than 5% soluble in soy oil. Terbutaline sulfate (see U.S. 6,544,542), oestriol and amino-1-phenylpropanol (see the Merck Index), nitroglycerin (see Therapeutics: Its Principles and Practice, by Horatio C. Wood, p. 333), acetylsalicylic acid (Subrananian et al., International Immunopharmacology (2008) 8, 1533) and benzylpenicillin are all known to be soluble in liquid fats. Thus, in reality, the Examples of Engstrom teach away from the solubilization of drugs that are difficultly soluble, in particular poorly soluble in soy oil.

Examiner cites Unger as curing the defects of Engstrom because Unger "teach[es] solubilizing agents for use with a delivery vehicle." This is an incorrect statement. What Unger actually states is: "For topical applications, the steroid products may be used alone, may be mixed with one or more solubilizing agents **or** may be used with a delivery vehicle, and applied to the skin or mucosal membranes." (Column 79, Lines 57-60; Emphasis supplied). From this language it is clear that Unger suggests three alternative approaches, and in the alternative

involving the solubilizing agent, the solubilizing agent serves as the medium for dissolving the steroid prodrug. This is a use which is well known to those skilled in the art in the topical skin administration of various compounds, for such benefits as fragrance enhancers, skin lubricants and permeation enhancers. While this is one way of delivering a steroid prodrug, it is a separate and alternative method to using a delivery vehicle such a reversed cubic phase system. Significantly, Unger offers no suggestion that a solubilization/penetration agent could be used in connection with any drug delivery vehicle, let alone that it would impact the incorporation of a prodrug (or other pharmaceutical active) into a delivery vehicle, let alone what the nature of the impact may or may not be on the phase behavior of the system. Indeed, to the extent Unger speaks to delivery of the difficult to solubilize steroid, Unger teaches away from the present Application, as Unger's entire approach is to promote the incorporation of steroids in lipid delivery systems by modifying the steroid itself, that is, by "covalently bonding to the steroid a lipid moiety via a linking group" (Column 2, Lines 5-6). Derivatizing the steroid in this way increases the lipophilicity of the steroid, and permits its ready incorporation into stabilizing materials such as emulsions. (Column 18, Line 14-23). Applicant notes that while chemical modification of the steroid to promote solubility may be effective, the resulting compound is most certainly a New Chemical Entity, and this significantly increases the regulatory hurdles to approval for pharmaceutical use.

By contrast, in the present Application the active pharmaceutical is not changed; rather, the lipid membrane of the drug delivery vehicle is altered by the incorporation of an essential oil or tocopherol so that composition in its entirety takes on the phase behavior of a reversed cubic phase structured fluid capable of incorporating the unchanged active at high loadings. Further, the components of the delivery vehicle are GRAS.

During the telephone interview of December 10, 2009, The Examiner referred specifically to lines 29-34 of column 80 of Unger: "The penetrating/solubilizing agents may or may not be in a base which can be composed of various substances known to those skilled in the art, including, for example, glycerol, propylene glycol; isopropyl myristate; urea in propylene glycol, ethanol and water; and polyethylene glycol (PEG)." Applicant notes that this section still relates to the narrow aspect of topical delivery, and as such suggests merely mixtures of a few substances known for that purpose, without any discussion of the desirability or challenges of producing structured fluids with high loading capacities for difficultly soluble pharmaceutical

agent. In addition, the Examiner also specifically inquired whether or not the cubic phase of Engstrom would be maintained if an essential oil or tocopherol (e.g. such as listed by Unger) was added thereto. In the Declaration of the inventor, Dr. Anderson, provided herewith, Dr. Anderson avers that if an essential oil or tocopherol were added to the cubic phase of Engstrom, the cubic phase typically would not be maintained. Instead, one of two possible outcomes would ensue. Either A) the essential oil or tocopherol would not be taken up; or B) the cubic phase structure of the material would be liquefied. Such a hypothetical "combination" of Engstrom and Unger is thus generally not viable since the combination would either not be combinable, or would destroy the claimed and required properties of the Engstrom material.

Applicant further notes that Unger's teaching is merely a passing mention in a lengthy patent of three essential oils buried in an extensive list of classes of compounds and specific compounds identified as "penetrating and /or solubilizing agents useful for the topical application of the steroidal drug product." (Col 79, Lines 60-61.), and as discussed above, Unger thus teaches such solubilization/penetration agents for use in a separate and distinct approach from use with a delivery vehicle. Of course, with this focus, Unger makes no mention or suggestion of the impact of such substances on the phase behavior of structured fluids or the incorporation of compounds in structured fluids, reversed cubic phase structured fluids in particular. It is Applicant's position that this teaching thus falls short of obviousness under the Court's decision in *In re* Kubin. Kubin states that it is improper to reject claims based on purported obviousness when one of skill in the art would need to try numerous combinations of ingredients, e.g. from a "laundry list" of possible ingredients, when the reference provides no additional guidance for selection of components. Applicant has studied the section of Unger referred to by Examiner (columns 79-80, lines 57-67 and 1-34) and notes that "essential oils of eucalyptus, chenopodium and yang ylang" make up only one phrase in an extensive and varied list of scores of possible solubilizing agents which also includes pyrrolidones, fatty acids, amines and derivatives, surfactants, alcohols, glycols, and others, with no emphasis or guidance regarding how one would preferentially select one above any other for use as a solubilizer, and of course no guidance regarding "inclusion" in a "delivery vehicle" of which a large number of different types are also listed (see lines 15-26 of column 6). Further, essential oils are listed as suitable only for inclusion in formulations for topical delivery (see line 57 of column 79), not for any other use, e.g., in formulations that are injectable; and, to repeat, separate from the use with a

delivery vehicle. Nor does Unger describe or allude to difficultly soluble substances, and certainly not the specific characteristics and challenges involving those certain active pharmaceutical agents as defined in the present Application. .

Applicant submits that in light of these observations, the present invention as claimed herein in not rendered obvious in view of Engstrom and Unger, and respectfully requests reconsideration and withdrawal of this rejection.

New Claims

New claims 70-72, 77-78, 83-84 and 102-103 recite particular ratios of phospholipid to essential oil, support being found in paragraph [0219] of the published application. The attached Table provides Examiner with a convenient index of the location, within the specification, of support for these new claims.

New claims 72, 79 and 85 recite that the pharmaceutical active is equal to or greater than 5% soluble in said essential oil or tocopherol, supported in the table in paragraph [0235].

New claims 73, 80 and 86 recite that the composition is suitable for injection, supported by paragraphs [0206], [0251], and [0293].

New claims 74, 81, and 87 recite particular types of pharmaceutical actives, and new claims 75, 82 and 88 recite particular pharmaceutical actives. Support for the agents listed in these claims are found in the application as filed, for example, in Tables 1 and 2

New claims 76 and 89 recite particular essential oils that may be used in the practice of the invention. Support for this recitation is found, for example, in the paragraph [0210] of the published application.

New claims 90-92 recite that the phospholipid may comprise phosphatidylcholine, supported in paragraph [0230] of the published application.

New claims 93-94 recite that the tocopherol may comprise alpha-tocopherol, supported in paragraph [0285] of the published application.

New claims 95-97 recite that the reversed cubic phase is bicontinuous, supported, e.g. in paragraphs [0116] - [0120] of the published application.

New claims 98-101 are similar to claims 66-68 and require the formation of a reversed cubic liquid crystalline phase from water, phospholipids, essential oils or tocopherol, and, depending on the formulation, difficult to solubilize pharmaceutical actives. See Example 1.

New claims 104-107 further require that the difficult to solubilize pharmaceutical active would otherwise require 100 ml of water to solubilize a single dose. This is discussed in paragraph [0020]. Thus, the invention provides a mechanism to solubilize and deliver in a suitable formulation a very difficult to solubilize drugs.

New claims 108-111 further require that the reversed cubic liquid phase material exists at body temperature. This is shown in Example 1 at paragraph [0285]. Thus, the formulations described herein can be used to effectively deliver the difficult to solubilize pharmaceutical active to the patient, e.g., systemically.

Applicant respectfully submits that none of these new claims adds any new matter to the application, and requests their entry, examination and allowance.

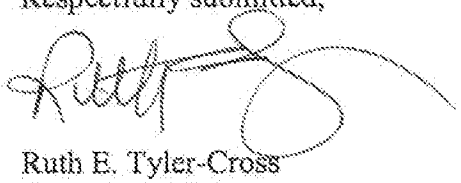
Concluding Remarks

In view of the foregoing, it is requested that the application be reconsidered, that claims 66-68 and 70-111 be allowed, and that the application be passed to issue.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at 703-787-9400 (fax: 703-787-7557; e-mail: ruth@wcc-ip.com) to discuss any other changes deemed necessary in a telephonic or personal interview.

If an extension of time is required for this response to be considered as being timely filed, a conditional petition is hereby made for such extension of time. Please charge any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,



Ruth E. Tyler-Cross
Reg. No. 45,922

Whitham, Curtis, Christofferson & Cook, P.C.
11491 Sunset Hills Road, Suite 340
Reston, VA 20190
703-787-9400 (Telephone)
703-787-7557 (Facsimile)
Customer No. 30743

References in Specification US2002 0102280 on which New Claims are based

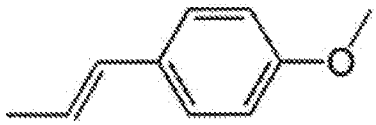
#	Matter	Reference
70 77 83 102 103	Ratio of phospholipid to essential oil is from 0.5:1 to 1.5:1. (same for tocopherol)	Paragraph [219] "Ratios between about 1:2 and about 1.5:1" equates to 0.5:1 and 1.5:1. Paragraph [230] "Thus, for example, when phosphatidylcholine is mixed with water and one of these aforesaid oils at a phosphatidylcholine: oil: water ratio of about 42:34:24, liquid crystals generally result at ambient temperatures. The ratio 42:34 PC to oil equates to 1.24:1. Also see Examples 7 (1.45:1) and 9 (1.26:1) Also see paragraph [0196] which references alpha tocopherol and essential oils as examples of dissolution/solubilization agents. It can be inferred that the same ratios apply for tocopherol as essential oils.
71 78 84	Ratio of phospholipid to essential oil is from 0.7:1 to 1.2:1. (same for tocopherol)	Paragraph [219] "most preferably between about 0.7:1 and about 1.2:1." Also see Examples 4 (1:09:1) and 8 (1.09:1). Also see paragraph [0196] which references alpha tocopherol and essential oils as examples of dissolution/solubilization agents. It can be inferred that the same ratios apply for tocopherol as essential oils.
72 79 85	Pharmaceutical active is equal to or greater than 5% soluble in an essential oil or tocopherol	Paragraph [0235], including Table, and [236]. Also see paragraph [0196] which references alpha tocopherol and essential oils as examples of dissolution/solubilization agents. It can be inferred that the same solubility characteristics apply for tocopherol as essential oils.
73 80 86	suitable for injection	Paragraphs [0006], [0206], [0283], and [0293]
74 81 87	 analgesics anesthetics antibiotics antifungals antineoplastic agents antiviral agents enzyme inhibitors hormones anticonvulsants immunosuppressants	Paragraph [0158] Table 1 and Paragraph [0159] Table 2 Table 1 1 1 2 1 2(cont) 2(cont) 2(cont) 1 2(cont)

	antipsychotics tumor necrosis factor (TNF) inhibitors	2 2(cont)
75 82 88	 Buprenorphine Chloramphenicol cyclosporin A daunorubicin erythromycin A fentanyl nitrazapem SN-38 Irinotecan bupivacaine.	Paragraph [0158] Table 1 and Paragraph [0159] Table 2 Table 2(cont) 1 2(cont) 2(cont) 1 2 1 2(cont) 2(cont) Paragraph [0306]
76 89	 Spearmint Ginger Clovebud Eucalyptus Peppermint anise seed balsam of Peru coriander orange santalwood.	Paragraph [0221] [0224] [0214] [0212] [0220] [0212] [0212] [0212] [0212] [0212] [0212]
104-107	require 100 ml of water to solubilize a single therapeutic dose	[0020]
68 101 108-111	stability at body temperature	[0285]
90 91 92	phosphatidylcholine	Paragraphs [0230] and [0272]
93 94	alpha-tocopherol	Paragraphs [0204], [0205] and [0285]
95 96 97	reversed cubic phase is bicontinuous	Paragraphs [0116] - [0120]
98	Composition described throughout the application with essential oil	Paragraph [0008], Examples 4 and 7
99	Composition described throughout the application with tocopherol	Example 1.
100	mixtures of one or more essential oils mixtures of one or more essential oils and tocopherol	Paragraph [0211], Example 8 Paragraph [0205], Example 3
102	Internally administrable solvent system	Paragraph [0010]

Anethole

From Wikipedia, the free encyclopedia

Anethole (also **para methoxy phenyl propene**, **p-propenylanisole,** and **isoestragole**) is an aromatic compound that occurs widely in nature, in essential oils. It contributes a large component of the distinctive flavors of anise and fennel (both in the botanical family Apiaceae), anise myrtle (Myrtaceae), licorice (Fabaceae), and star anise (Illiciaceae). Closely related to anethole is its double-bond isomer estragole, abundant in tarragon (Asteraceae) and basil (Lamiaceae), that has a flavor reminiscent of anise. Anethole has numerous commercial uses in multiple industries, and high potential for additional uses.

Anethole	
	
IUPAC name	1-methoxy-4-(1-propenyl)benzene
Identifiers	
CAS number	104-46-1 ✓
PubChem	637563
SMILES	O(c1ccc(\C=C\C)cc1)C
InChI	1/C10H12O/c1-3-4-9-5-7-10(11-2)8-6-9/h3-8H,1-2H3/b4-3+
InChI key	RUVINXPYWBROJD-ONEGZZNKBR
ChemSpider ID	553166
Properties	
Molecular formula	$C_{10}H_{12}O$
Molar mass	148.2 g mol^{-1}
Density	0.998 g/cm^3
Melting point	20-21 °C
Boiling point	234 °C; 81 °C at 2 mmHg
Hazards	
MSDS	External MSDS (http://physchem.ox.ac.uk/MSDS/AN/anethole.html)
Related compounds	
Related compounds	Anisole; Estragole
✓ (what is this?) (verify) (http://en.wikipedia.org/w/index.php?title=Anethole&diff=cur&oldid=321809583) Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	

Contents

Structure and properties

Chemically, anethole is an aromatic, unsaturated ether. It has two cis-trans isomers (see also E-Z notation), involving the double bond outside the ring. The more abundant isomer, and the one preferred for use, is the *trans* or *E* isomer: ***trans*-anethole**, **t-anethole**, **(E)-anethole**, **trans-para methoxy phenyl propene**. Its full chemical name is *trans*-1-methoxy-4-(prop-1-enyl)benzene.

Anethole is less soluble in water than in ethanol, which causes certain anise-flavored liquours to become opaque when diluted with water (see Ouzo effect). It is a clear, colorless liquid with boiling point 234 °C

and congealing point (freezing point) 20 °C;[1] below its congealing point, anethole forms white crystals. The crystals will precipitate from an aqueous solution, which causes a "snow globe" effect when certain anise-flavored liquours are chilled. This effect is the basis of a patent for industrial purification of anethole from sources such as pine oil.[2] Anethole can be crystallized directly from a source essential oil by lowering the temperature of the oil; adding a crystal of anethole helps to start the process.[3] Historically, this was used to detect adulteration.[4]

Production

Commercial sources of anethole include some essential oils:[5]

Essential oil	World production	*trans*-anethole
Anise	8 tons (1999)	95%
Star anise	400 tons (1999), mostly from China	87%
Fennel	25 tons (1999), mostly from Spain	70%

Uses

Anethole is a flavoring substance of commercial value. In addition, it is distinctly sweet, measuring 13 times sweeter than sugar. It is perceived as being pleasant to the taste even at higher concentrations. It is unrelated to glycyrrhizic acid, which often co-occurs with it, and also is very sweet. Anethole is used in alcoholic drinks, seasoning and confectionery applications, oral hygiene products, and in small quantities in natural berry flavors.[5]

Anethole is an inexpensive chemical precursor for paramethoxyamphetamine (PMA),[6] and used in its clandestine manufacture.[7] Anethole is present in the essential oil from guarana, which is alleged to have has a psychoactive effect; however, the absence of PMA or any other known psychoactive derivative of anethole leads to the conclusion that any purported psychoactive effect of guarana is not due to anethole.[8] Anethole is also present in absinthe, a liquor with a reputation for psychoactive effects; these effects however are attributed to ethanol[9] (see also Thujone).

Pharmaceutical drugs derived from or related to anethole include anisyldithiolthione,[10] anethole dithione (ADT), and anethole trithione (ATT).

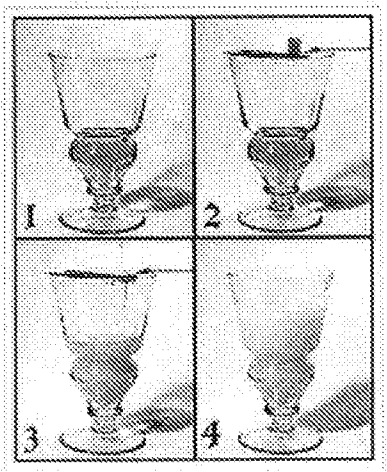
Research

Anethole is responsible for the "ouzo effect", the spontaneous formation of a microemulsion[11][12] that gives many alcoholic beverages containing anethole and water their cloudy appearance. Such a spontaneous microemulsion has many potential commercial applications in the food and pharmaceutical industries.[13] A derivative of anethole, anethole trithione, is being investigated for use in self-microemulsifying drug delivery systems (SMEDDS).[14]

Bacterial strains capable of using trans-anethole as the sole carbon source include JYR-1 (*Pseudomonas putida*)[15] and TA13 (*Arthrobacter aurescens*).[16] Because they metabolize anethole into several aromatic chemical compounds, these bacteria are candidates for use in commercial bioconversion of

these valuable compounds from anethole and other phenylpropanoids. Compared to other industrial processes, such bioconversion may be less costly and more friendly to the environment.[16]

Anethole has potent antimicrobial properties, against bacteria, yeast, and fungi.[17] Reported antibacterial properties include both bacteriostatic and bactericidal action against *Salmonella enterica*[18] but not when used against *Salmonella* via a fumigation method.[19] Antifungal activity includes increasing the effectiveness of some other phytochemicals (eg polygodial) against *Saccharomyces cerevisiae* and *Candida albicans*;[20] this synergistic effect has potential medical uses.[21]



Diluting absinthe with water produces a spontaneous microemulsion (ouzo effect)

In vitro, anethole has antihelmintic action on eggs and larvae of the sheep gastrointestinal nematode *Haemonchus contortus*.[22] Anethole also has nematicidal activity against the plant nematode *Meloidogyne javanica* in vitro and in pots of cucumber seedlings.[23]

Anethole also is a promising insecticide. Several essential oils consisting mostly of anethole have insecticidal action against larvae of the mosquitos *Ochlerotatus caspius*[24] and Aedes aegypti.[25][26] Similarly, anethole itself is effective against the fungus gnat *Lycoriella ingenua* (Sciaridae)[27] and the mold mite *Tyrophagus putrescentiae*.[28] Against the mite, anethole is a slightly more effective pesticide than DEET but anisaldehyde, a related natural compound that occurs with anethole in many essential oils, is 14 times more effective.[28] The insecticidal action of anethole is greater as a fumigant than as a contact agent. (E)-anethole is highly effective as a fumigant against the cockroach *Blattella germanica*[29] and against adults of the weevils *Sitophilus oryzae*, *Callosobruchus chinensis* and beetle *Lasioderma serricorne*.[30]

As well as an insect pesticide, anethole is an effective insect repellent against mosquitos.[31]

Safety

Formerly generally recognized as safe (GRAS), after a hiatus anethole was reaffirmed by Flavor and Extract Manufacturers Association (FEMA) as GRAS.[32] The hiatus was due to concerns about liver toxicity and possible carcinogenic activity, reported in rats.[33] Anethole is associated with a slight increase in liver cancer in rats,[33] although the evidence is scant and generally regarded as evidence that anethole is *not* a carcinogen.[33][34] An evaluation of anethole by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) found its notable pharmacologic properties to be reduction in motor activity, lowering of body temperature, and hypnotic, analgesic, and anticonvulsant effects.[35] A subsequent evaluation by JECFA found some reason for concern re carcinogenicity but insufficient data.[36] At this time, the JECFA summary of these evaluations is that anethole has *no safety concern at current levels of intake when used as a flavoring agent*.[37]

In large quantities, anethole is slightly toxic and may act as an irritant.[38]

See also

- Category:Anise liqueurs and spirits
- List of liqueurs#Anise-flavored liqueurs
- Chavicol
- Safrole
- Fenchone

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External links

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Retrieved from "http://en.wikipedia.org/wiki/Anethole"
Categories: Flavors | Sweeteners | Essential oils | Phenylpropanoids | Ethers | Aromatic compounds

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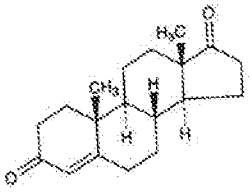
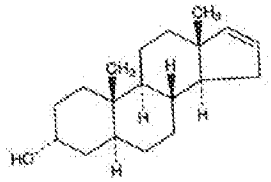


Dimorphous. Needles from acetone, mp 142-144°; crystals from hexane, mp 173-174°. $[\alpha]_D^{26}$ +191° (alc). uv max: 235 nm.

Dioxime, $C_{19}H_{28}N_2O_2$, crystals, mp 143°.

3-Semicarbazone, $C_{20}H_{29}N_3O_2$, crystals, dec 245°.

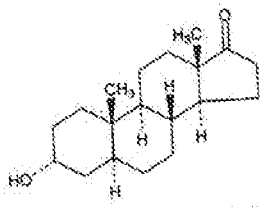
679. (3α,5α)-Androst-16-en-3-ol. 3α-Hydroxy-5α-androst-16-ene; Δ^{16}-androsten-3-ol. $C_{19}H_{30}O$; mol wt 274.45. C 83.15%, H 11.02%, O 5.83%. A major constituent of boar pheromone, having a pronounced musk-like odor. Isoln from swine testes: V. Prelog, L. Ruzicka, *Helv. Chim. Acta* **27**, 61 (1944). Prepn: V. Prelog *et al.*, *ibid.* 66; J. Fishman *et al.*, *J. Org. Chem.* **28**, 1443 (1963). Physiological role as a sex attractant for pigs: D. B. Gower, *J. Steroid Biochem.* **3**, 45 (1972). Use in pig artificial insemination: D. R. Melrose *et al.*, Ger. pat. **1,937,264** corresp to U.S. pat. **3,681,490** (1970, 1972 both to Nat. Res. Dev. Corp.). *In vivo* metabolism in boar testes: Y. A. Saat *et al.*, *Biochem. J.* **144**, 347 (1974). It has also been detected in human male axillary sweat, but has no androgenic activity: B. W. L. Brooksbank *et al.*, *Experientia* **30**, 864 (1974). Radioimmunoassay: D. C. Bickell, D. B. Gower, *J. Steroid Biochem.* **7**, 451 (1976). Receptor studies: J. N. Gennings *et al.*, *Biochim. Biophys. Acta* **496**, 547 (1977). Biosynthetic studies: E. L. Hurden *et al.*, *J. Endocrinol.* **81**, 161P (1979); G. M. Cook, D. B. Gower, *ibid.* **88**, 409 (1981). Discovery of the presence of androst-16-en-3-ol in truffles *(Tuber melanosperum)* has been offered as an explanation for the ability of pigs to detect truffles growing as deep as 1 meter underground: R. Claus *et al.*, *Experientia* **37**, 1178 (1981).



Crystals, mp 142.5-143°. Purified by sublimation in high vacuum and recryst from acetone. $[\alpha]_D^{20}$ +13.1° (c = 0.957 in chloroform). Gives a blue color in the Kägi-Miescher test, *cf. Helv. Chim. Acta* **22**, 683 (1939).

USE: As an aid to estrus determn in pig artificial insemination.

680. Androsterone. *(3α,5α)-3-Hydroxyandrostan-17-one; cis*-androsterone; 3α-hydroxy-17-androstanone; androstan-3α-ol-17-one; 3α-hydroxyetiocholan-17-one; 3-epihydroxyetiocholan-17-one. $C_{19}H_{30}O_2$; mol wt 290.45. C 78.57%, H 10.41%, O 11.02%. Isolation from male urine after removal of the phenolic estrogen fraction: Butenandt, Tscherning, *Z. Physiol. Chem.* **229**, 167 (1934); v. Euw, Reichstein, *Helv. Chim. Acta* **25**, 988 (1942). Prepn from cholesterol: Ruzicka, *ibid.* **17**, 1389 (1934); Marker, *J. Am. Chem. Soc.* **57**, 1755 (1935); Schoeller *et al.*, U.S. pat. **2,-232,735** (1941 to Schering).



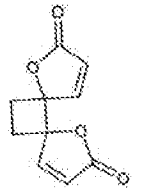
Crystals from acetone-ether, mp 185-185.5°. Sublimes in high vacuum. $[\alpha]_D^{20}$ +94.6° (c = 0.7 in abs alc). $[\alpha]_D^{25}$ +87.8° (c = 1.5 in dioxane). Not precipitated by digitonin. Barely soluble in water. Sol in most organic solvents.

Acetate, $C_{21}H_{32}O_2$, crystals from ether, sublimes in high vac, mp 165°, $[\alpha]_D^{24}$ +76.7° (c = 2.04 in dioxane); $[\alpha]_D^{25}$ +86° (c = 2 in ethanol).

Propionate, $C_{22}H_{34}O_2$, mp 151-152°.

Benzoate, $C_{26}H_{34}O_2$, mp 178°.

681. Anemonin. *trans-1,7-Dioxadispiro[4.0.4.2]dodeca-3,9-diene-2,8-dione;* 1,2-dihydroxy-1,2-cyclobutanediacrylic acid di-γ-lactone; Anemone camphor; Pulsatilla camphor. $C_{10}H_8O_4$; mol wt 192.17. C 62.50%, H 4.20%, O 33.30%. Found in *Anemone pulsatilla* L. and other *Ranunculaceae*. Its precursor in plants is protoanemonin. Isoln from *Ranunculus acer*: Zecher, Wohlmuth, *Sci. Pharm.* **22**, 95 (1954); *C.A.* **48**, 13169b (1954). Structure: Moriarty *et al.*, *J. Am. Chem. Soc.* **87**, 3251 (1965); Romain, *Diss. Abstr. B* **27**, 3867 (1967). Synthesis: Sugiyama *et al.*, *C.A.* **67**, 116604n (1967). Toxicity study: R. Brodersen, A. Kjaer, *Acta Pharmacol.* **2**, 109 (1946).



Crystals from petr ether, mp 157-158°. Volatile with steam. Slightly sol in cold, more in hot water; sol in hot alcohol, chloroform, alkalies with yellow color. Practically insol in ether. LD_{50} i.p. in mice: 150 mg/kg (Brodersen, Kjaer).

Note: Not to be confused with anemonine which is 5-(carboxymethyl)-1,1-dimethylimidazolium hydroxide inner salt.

682. Anethole. *1-Methoxy-4-(1-propenyl)benzene; p-propenylanisole;* anise camphor; Monasirup. $C_{10}H_{12}O$; mol wt 148.20. C 81.04%, H 8.16%, O 10.80%. Chief constituent of anise, star anise and fennel oils: Monad, de Dortan, *Compt. Rend. Ind. Parfum.* **5**, 401 (1950); Naves, Tucakov, *Compt. Rend.* **248**, 843 (1959). Separation of *cis* and *trans* isomers: Naves *et al.*, *ibid.* **246**, 1734 (1958); *Bull. Soc. Chim. France* **1958**, 566; Naves, *Helv. Chim. Acta* **43**, 230 (1960); Ferroni *et al.*, *Gazz. Chim. Ital.* **92**, 1198 (1962). Synthesis: Mueller, Rösch eisen, *Ber.* **90**, 543 (1957); R. J. DePasquale, *Synth. Commun.* **10**, 223 (1980). Toxicity: J.-R. Boissier *et al.*, *Therapie* **22**, 309 (1967). *Review:* Wagner, *Mfg. Chemist* **23**, 56 (1952).

trans - isomer

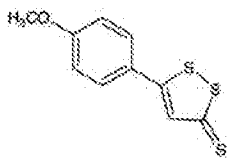
trans-Isomer, crystalline mass at 20-21°, mp 21.4°. Liquid above 23°. d_4^{30} 0.9883, $bp_{2.5}$ 81-81.5°, n_D^{30} 1.56145. uv max (ethanol): 259 nm (ε 22300). Practically insol in water. Misc with ether, chloroform; sol in benzene, ethyl acetate, acetone, carbon disulfide, petr ether; 1 ml dissolves in 2 ml alc. LD_{50} i.p. in rats: 900 mg/kg (Boissier).

cis-Isomer. d_4^{30} 0.9878, $bp_{2.5}$ 79-79.5°, n_D^{30} 1.55455. uv max (ethanol): 253.5 nm (ε 18500). LD_{50} i.p. in rats: 93 mg/kg (Boissier).

USE: Manuf anisaldehyde; flavoring agent; in perfumery, particularly for soap and dentifrices; sensitizer in bleaching colors in color photography; as an imbedding material in microscopy. Pharmaceutic aid (flavor).

THERAP CAT (VET): Has been used as a carminative.

683. Anethole Trithione, *5-(p-Methoxyphenyl)-3H-1,2-dithiole-3-thione;* 3-(*p*-anisyl)trithione; 3-(*p*-methoxyphenyl)-4,5-dithiacyclopent-2-ene-1-thione; 3-(*p*-anisyl)-4,5-dithiacyclopent-2-ene-1-thione; (*p*-methoxyphenyl)trithiopropene; trithio-*p*-methoxyphenylpropene; 5-(*p*-methoxyphenyl)-1,2-dithiacyclopent-4-ene-3-thione; 3-(*p*-methoxyphenyl)trithione; trithioanethole; Heporal; Mucanol; Trithio; Sufralem; Tiotrifar; Felvites; Sulfogal; Sulfarlem. $C_{10}H_8OS_3$, mol wt 240.37. C 49.97%, H 3.35%, O 6.66%, S 40.02%. Prepn: Böttcher, Lüttringhaus, *Ann.* **557**, 89 (1947); Gaudin, Lozac'h, *Compt. Rend.* **224**, 557 (1947); Lüttringhaus *et al., Ann.* **560**, 201 (1948); Gaudin, U.S. pats. **2,556,963, 2,688,620** (1951, 1954); Böttcher, Ger. pats. **855,865, 869,799** and **874,447** (1952 and 1953); Thuiller, Vialle, *Bull. Soc. Chim. France* **1959**, 1398.



Orange-colored prisms from butyl acetate. Very bitter taste. mp 111°. Practically insol in water. Sol in pyridine, chloroform, benzene, dioxane, carbon disulfide. Slightly sol in ether, acetone, ethyl acetate, acetic acid, alc, cyclohexane, petr ether.

Oxime, $C_{10}H_9NO_2S_3$, yellow needles, mp 170°. Soluble in dioxane.

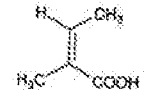
Methiodide, yellow crystals, mp 189°.

THERAP CAT: Choleretic.

684. Angelica. Fruit or root of *Angelica archangelica* L. (*A. officinalis* Moench.). *Umbelliferae. Habit.* Europe, Asia. *Constit.* Roots: Volatile oil (0.3-1%), angelic acid, 6% resin, angelicol, angelicin, xanthotoxol, starch, osthole, osthenol, archangelicin, archangin, sitosterol, and acids such as aconitic, malic, quinic, chlorogenic, caffeic, fumaric, citric, angelic, and oxalic. Fruit: About 1% volatile oil, bitter substance, coumarins, resin. *Refs:* Späth, Pesta, *Ber.* **67**, 853 (1934); Späth, Vierhapper, *ibid.* **70**, 248 (1937); Svendsen, *C.A.* **52**, 2173g (1958); Sroka, *Apoth.-Ztg.* **61**, 37 (1949).

THERAP CAT: Carminative, diaphoretic, diuretic.

685. Angelic Acid. *(Z)-2-Methyl-2-butenoic acid; cis*-2-dimethylcrotonic acid; 2-methylisocrotonic acid; *cis*-2,3-dimethylacrylic acid. $C_5H_8O_2$, mol wt 100.12. C 59.98%, H 8.05%, O 31.96%. Stereoisomer of tiglic acid. Found in ester form in sumbul root, *Angelica archangelica* L., *Umbelliferae* and together with tiglic acid esters in the oil of the Roman camomile, *Anthemis nobilis* L., *Compositae.* Isoln from seeds of *Schoenocaulon officinale* (Lindl.) A. Gray, *Liliaceae* (cevadilla seeds) by alkaline hydrolysis of cevadine: Stoll, Seebeck, *Helv. Chim. Acta* **35**, 1275 (1952). Synthesis by *trans* addition of bromine to tiglic acid: Buckles, Mock, *J. Org. Chem.* **15**, 680 (1950). Review and bibliography: Buckles *et al., Chem. Rev.* **55**, 659 (1955).



Monoclinic rods, needles, plates; mp 45°. Spicy odor. *Vesicant.* d_4^{47} 0.983, bp_{760} 185°; bp_{12} 86°. Sublimes. Volatile with steam. n_D^{47} 1.4434. K at 25° = 5.0×10^{-5}. uv max (H_2O): 217 nm (ε 5.15×10^3). Molar heat of combustion 626.6 kcal. Sparingly soluble in cold water, freely sol in hot water. Sol in alcohol, ether. Prolonged boiling of aq soln causes isomerization to tiglic acid; the process is speeded up by traces of bromine and sunlight, also by strong mineral acids or alks. Dry crystals of angelic acid have been stored in bottles for years without evidence of isomerization.

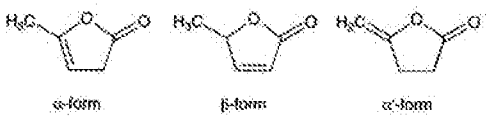
Calcium salt dihydrate, $Ca(C_5H_7O_2)_2.2H_2O$, leaflets. Much more soluble in water than calcium tiglate: 100 parts of aq soln satd at 17.5° contains 23 parts of anhydr calcium angelate.

Amide, C_5H_9NO, crystals, mp 127-128°.

Methyl ester, $C_6H_{10}O_2$, liquid; d_4^{20} 0.9413; bp_{760} 128°; n_D^{20} 1.4321.

Ethyl ester, $C_7H_{12}O_2$, liquid; $d_4^{0.5}$ 0.9178; bp_{760} 141.5°; bp_{11} 49°. n_D^{20} 1.4304. Heat of formn at constant vol 963.1 kcal, at constant press. 964.2 kcal.

686. Angelica Lactone. *5-Methyl-2-furanone.* $C_5H_6O_2$; mol wt 98.10. C 61.22%, H 6.16%, O 32.62%. Exists in three forms. Prepn of α and β-forms: Wolff, *Ann.* **229**, 250 (1885); Thiele, *Ann.* **319**, 184 (1901); v. Auwers, *Ber.* **56**, 1672 (1923); J. H. Helberger *et al., Ann.* **561**, 215 (1949). Prepn of α'-form: J. P. Wineburg *et al., J. Heterocycl. Chem.* **12**, 749 (1975); V. Jäger, H. J. Günther, *Tetrahedron Letters* **1977**, 2543; R.A. Amos, J. A. Katzenellenbogen, *J. Org. Chem.* **43**, 560 (1978). Toxicity data for α-form: E. J. Moran *et al., Drug Chem. Toxicol.* **3**, 249 (1980).



α-Form, *5-methyl-2(3H)-furanone, Δ²-angelica lactone, γ-methyl-β,γ-crotonolactone, 4-hydroxy-3-pentenoic acid γ-lactone.* Volatile needles, mp 18°. d_4^{20} 1.084. bp_{12} 56°. n_{He}^{20} 1.4476. One gram dissolves in 20 ml water at 15°. Heating with triethylamine soln converts it to the β-form. LD_{50} orally in mice: 2800 mg/kg (Moran).

β-Form, *5-methyl-2(5H)-furanone, Δ¹-angelica lactone, γ-methyl-α,β-crotonolactone, 4-hydroxy-2-pentenoic acid γ-lactone.* Liquid. Not solidified at −17°. d_4^{20} 1.076. bp_{751} 208-209°. bp_{16} 87°. n_{He}^{20} 1.4603. Sol in water. Forms a dimer. More stable than α-form.

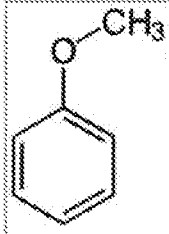
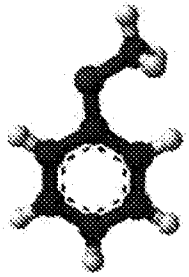
α'-Form, *dihydro-5-methylene-2(3H)-furanone, γ-methylene-γ-butyrolactone.* bp_{17} 80°.

687. Angiogenin. Single-chain, basic protein of 123 amino acids that induces the *in vivo* formation of blood vessels. Mol wt ~14,000 Da. First isolated from human adenocarcinoma cells; subsequently found in normal human plasma and shown to be produced by the liver. Angiogenin exhibits a characteristic ribonucleolytic activity toward 28S and 18S ribosomal RNA. Its amino acid sequence is 35% identical with that of human pancreatic ribonuclease. Isoln, characterization, and angiogenic activity: J. W. Fett *et al., Biochemistry* **24**, 5480 (1985). Amino acid sequence: D. J. Strydom *et al., ibid.* 5486. Cloning and DNA sequence of human angiogenin gene: K. Kurachi *et al., ibid.* 5494. Structural study: K. A. Palmer *et al., Proc. Nat. Acad. Sci. USA* **83**, 1965 (1986). Ribonucleolytic activity: R. Shapiro *et al., Biochemistry* **25**, 3527 (1986). Isoln from normal human plasma: R. Shapiro *et al., ibid.* **26**, 5141 (1987). Tissue distribution in neonatal and adult rats: H. L. Weiner *et al., Science* **237**, 280 (1987); in human tumor and normal cells: S. M. Rybak *et al., Biochem. Biophys. Res. Commun.* **146**, 1240 (1987). Inhibition of protein synthesis: D. K. St. Clair *et al., Proc. Nat. Acad. Sci. USA* **84**, 8330 (1987). Inhibition of angiogenic and ribonucleolytic activities of angiogenin by placental ribonuclease inhibitor: R. Shapiro, B. L. Vallee, *ibid.* 2238; F. S. Lee, B. L. Vallee, *Biochemistry* **28**, 3558 (1989). *Reviews:* J. F. Riordan, B. L. Vallee, *Brit. J. Cancer* **57**, 587-590 (1988); B. L. Vallee, J. F. Riordan, *Adv. Exp. Med. Biol.* **234**, 41-53 (1988).

Anisole

From Wikipedia, the free encyclopedia

Anisole is the organic compound with the formula $CH_3OC_6H_5$. This colorless liquid has a smell reminiscent of anise seed. It is used as a precursor to other organic compounds. Substituted derivatives are also called anisoles.

Anisole	
	
IUPAC name	Anisole [2] (http://www.chemindustry.com/apps/chemicals?m=s&t=Anisole)
Other names	methoxybenzene and phenoxymethane
Identifiers	
CAS number	100-66-3 ✓
SMILES	COc1ccccc1
Properties	
Molecular formula	C_7H_8O
Molar mass	108.14 g/mol
Density	0.995 g/cm³
Melting point	−37 °C
Boiling point	154 °C
✓ (what is this?) (verify) (http://en.wikipedia.org/w/index.php?title=Anisole&diff=cur&oldid=305265640) Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	

Contents

Reactivity

Anisole undergoes electrophilic aromatic substitution reaction more quickly than does benzene, which in turn reacts more quickly than nitrobenzene. The methoxy group is an ortho/para directing group, which means that electrophilic substitution preferentially occurs at these three sites. The enhanced nucleophilicity of anisole vs benzene reflects the influence of the methoxy group, which renders the ring more electron-rich. The methoxy group strongly affects the pi cloud of the ring, moreso than the inductive effect of the electronegative oxygen.

Illustrative of its nucleophilicity, anisole reacts with acetic anhydride to give 4-methoxyacetophenone:

$$CH_3OC_6H_5 + (CH_3CO)_2O \rightarrow CH_3OC_6H_4C(O)CH_3 + CH_3CO_2H$$

Unlike most aromatic compounds and reflecting its high reactivity, the methoxyacetophenone undergoes a second acylation:

$$CH_3OC_6H_4C(O)CH_3 + (CH_3CO)_2O \rightarrow CH_3OC_6H_3(C(O)CH_3)_2 + CH_3CO_2H$$

Many related reactions have been demonstrated. For example, P_4S_{10} converts anisole to Lawesson's reagent, $[(CH_3O_6H_4)PS_2]_2$.

The ether linkage is highly stable, but the methyl group can be removed with hydroiodic acid:

$$CH_3OC_6H_5 + HI \rightarrow HOC_6H_4C(O)CH_3 + CH_3I$$

Preparation

Anisole is prepared by the Williamson ether synthesis, reacting sodium phenoxide with a methyl bromide and related reagents:[1]

$$2\ PhO^-Na^+ + CH_3Br \rightarrow CH_3OC_6H_5 + NaBr$$

Applications

Anisole is a precursor to perfumes, insect pheromones, and pharmaceuticals.[2] For example, synthetic anethole is prepared from anisole.

Safety

Anisole is relatively nontoxic with LD50 of 3700 mg/kg in rats.[3]

See also

- Anethole
- Bromoanisole
- Butylated hydroxyanisole
- Ether
- Ethyl phenyl ether
- Phenol
- 2,4,6-Trichloroanisole (cork taint)

References

1. ^ G. S. Hiers and F. D. Hager (1941), "Anisole (http://www.orgsyn.org/orgsyn/orgsyn/prepContent.asp?prep=cv1p0058) ", *Org. Synth.*, http://www.orgsyn.org/orgsyn/orgsyn/prepContent.asp?prep=cv1p0058; *Coll. Vol.* **1**: 58
2. ^ Helmut Fiege, Heinz-Werner Voges, Toshikazu Hamamoto, Sumio Umemura, Tadao Iwata, Hisaya Miki6, Yasuhiro Fujita, Hans-Josef Buysch, Dorothea Garbe, Wilfried Paulus "Phenol Derivatives" in Ullmann's Encyclopedia of Industrial Chemistry, 2002, Wiley-VCH, Weinheim. doi:10.1002/14356007.a19_313 (http://dx.doi.org/10.1002%2F14356007.a19_313)
3. ^ MSDS.[1] (http://www.seas.upenn.edu/~nanofab/chemicals/MSDS_Solvent_Anisole.pdf)

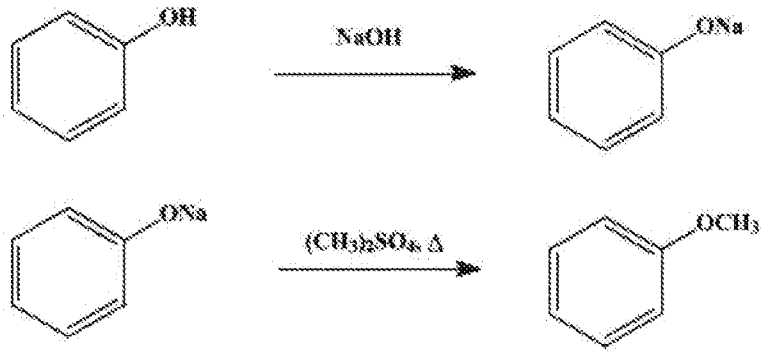
External links

- International Chemical Safety Card 1014 (http://www.inchem.org/documents/icsc/icsc/eics1014.htm)
- Pherobase (http://www.pherobase.com/database/compound/compounds-detail-anisole.php) pheromone database entry

Retrieved from "http://en.wikipedia.org/wiki/Anisole"
Categories: Flavors | Ethers | Aromatic compounds | Pheromones

Organic Syntheses, Coll. Vol. 1, p.58 (1941); Vol. 9, p.12 (1929).

ANISOLE



Submitted by G. S. Hiers and F. D. Hager.
Checked by Henry Gilman, S. A. Harris, and G. F. Wright.

1. Procedure

In a 5-l., three-necked, round-bottomed flask fitted with an efficient stirrer, separatory funnel, and reflux condenser is placed a mixture of 235 g. (2.5 moles) of phenol and 100 g. (2.5 moles) of sodium hydroxide (Note 1) in 1 l. of water. The mixture is cooled, with stirring, in an ice-salt bath to below 10°. There is then added through the separatory funnel, with stirring, 315 g. (235 cc., 2.5 moles) of dimethyl sulfate (Note 2). This addition requires about one hour, and the cooling bath is not removed until the addition is complete. The mixture is then heated on a water bath for one-half hour. At the end of this time there is added through the separatory funnel a mixture of 235 g. (2.5 moles) of phenol and 100 g. (2.5 moles) of sodium hydroxide in 1 l. of water. This addition requires about fifteen minutes. The mixture is then refluxed vigorously over a free flame for fifteen hours (Note 3).

The mixture is cooled and the anisole layer is separated. The aqueous portion is extracted with about 200 cc. of benzene (Note 4). The combined anisole-benzene portion is washed once with water, dried over calcium chloride and distilled from a modified Claisen flask (p. 130). The portion boiling at 100–153° is refractionated. The main fraction distils at 153–154°/748 mm. The yield is 388–405 g. (72–75 per cent of the theoretical amount) (Note 5) and (Note 6).

2. Notes

1. The sodium hydroxide was a high quality technical grade.

2. Dimethyl sulfate is toxic, but with due care to avoid spattering of the liquid and inhaling of the vapor the operation may be carried out without the use of a hood. Ammonia is a specific antidote for dimethyl sulfate and should be kept at hand to destroy any of the ester accidentally spilled.

A good technical grade of dimethyl sulfate was used.

3. When the period of refluxing is shorter, the yield is materially decreased. The first methyl group reacts easily but the second only with considerable difficulty. A longer period of refluxing does not give much larger yields. As the sodium sulfate concentration increases, the dimethyl sulfate hydrolyzes less readily.

It is recommended that the addition of dimethyl sulfate is best effected at the lowest temperature where reaction takes place readily. With phenol this is 25–35°. For

the second methyl group, the mixture is not refluxed but the anisole is boiled out, during which time the reaction completes itself (W. W. Hartman, private communication).

4. A separate fractional distillation of this benzene extract yields 9–18 g. of anisole. The major part of the anisole contained in the aqueous layer may be recovered by steam distillation instead of a benzene extraction. Neither method of recovery is wholly satisfactory.

5. When only one-half the amount of phenol is used, the yield is 85–92 per cent but with fairly inexpensive phenol it is more profitable to operate in such a manner that both methyl groups of the dimethyl sulfate are used.

6. Other methyl ethers may be prepared by a similar procedure. Methyl β-naphthyl ether is obtained in a 65–73 per cent yield by adding the dimethyl sulfate over a period of thirty minutes to equivalent quantities of β-naphthol and sodium hydroxide kept cool by an ice-water bath, then heating for one hour at 75–78°, and, finally, crystallizing from benzene to obtain the pure methyl ether which melts at 71°.

3. Discussion

Anisole can be prepared from phenol or its salts by the use of the following methylating agents: methyl chloride;[1] sodium methyl sulfate;[2] methyl alcohol in the presence of thorium oxide;[3] methyl alcohol and β-naphthalenesulfonic acid[4] or potassium hydrogen sulfate[5] or boron fluoride;[6] dimethyl sulfate;[2] and methyl ether and boron fluoride.[8]

References and Notes

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7. Lewis, Shaffer, Trieschmann, and Cogan, Ind. Eng. Chem. **22**, 34 (1930); Wolford, ibid. **22**, 397 (1930); Hodgson and Nixon, J. Chem. Soc. 2166 (1930).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

anisole-benzene

calcium chloride (10043-52-4)

ammonia (7664-41-7)

Benzene (71-43-2)

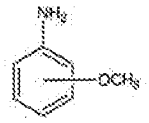
methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sodium sulfate (7757-82-6)

ß-naphthol (135-19-3)
Anisole (100-66-3)
dimethyl sulfate (77-78-1)
Methyl ß-naphthyl ether (93-04-9)
methyl ether (115-10-6)
methyl chloride (74-87-3)
sodium methyl sulfate (512-42-5)
thorium oxide
ß-naphthalenesulfonic acid (120-18-3)
potassium hydrogen sulfate (7646-93-7)
boron fluoride (7637-07-2)



***m*-Anisidine, 3-methoxybenzenamine, 3-methoxyaniline, 3-aminoanisole.** Pale yellow, oily liquid. Remains fluid even at −10°. bp 251°, bp_2 81-86°. Sparingly sol in water; sol in alc, acids.

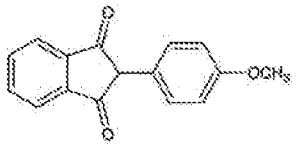
***o*-Anisidine, 2-methoxybenzenamine.** Yellowish liquid; becomes brownish on exposure to air. Volatile with steam. bp 225°, mp +5°. d_{15}^{15} 1.098. Practically insol in water. Miscible with alc, ether. *Keep well closed and protected from light.*

***p*-Anisidine, 4-methoxybenzenamine.** Crystals, mp 57°, bp 246°. Sparingly sol in water; freely sol in methanol, ethanol.

Note: *o*-Anisidine hydrochloride may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 93.

USE: In the manuf of azo dyes.

706. Anisindione. *2-(4-Methoxyphenyl)-1H-indene-1,3(2H)-dione;* 2-*p*-anisyl-1,3-indandione; 2-(*p*-methoxyphenyl)-1,3-indandione; SPE-2792; Miradon; Unidone. $C_{16}H_{12}O_3$; mol wt 252.27. C 76.18%, H 4.79%, O 19.03%. Prepn: Koelsch, *J. Am. Chem. Soc.* **58**, 1331 (1936); Horeau, Jacques, *Bull. Soc. Chim. France* **1948**, 53; Sperber, U.S. pat. **2,899,358** (1959 to Schering).



Pale yellow crystals from acetic acid or ethanol, mp 156-157°.

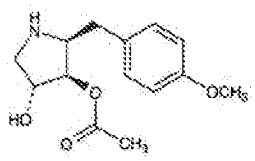
THERAP CAT: Anticoagulant.

707. Anisole, *Methoxybenzene.* C_7H_8O; mol wt 108.14. C 77.75%, H 7.46%, O 14.80%. $C_6H_5OCH_3$. Prepn from phenol and dimethyl sulfate: Ullmann, *Ann.* **327**, 114 (1903); Graebe, *Ann.* **340**, 204 (1905); G. S. Hiers, F. D. Hager, *Org. Syn.* **coll. vol. I**, 58 (2nd ed., 1941); from bromobenzene: Agfa, Ger. pat. **411,052**; *Chem. Zentr.* **1925, I**, 2411; *Frdl.* **15**, 193; by passing methyl chloride into a suspension of sodium phenolate in liquid ammonia: White *et al., J. Am. Chem. Soc.* **46**, 965 (1924); from phenol, methyl iodide and potassium carbonate in dimethylformamide: Brieger *et al., J. Chem. Eng. Data* **13**, 581 (1968). Forms oils or resins by condensation with formaldehyde: Ger. pats. **403,264**; **406,152**; *Chem. Zentr.* **1925, I**, 307, 1816; *Frdl.* **14**, 626, 627. Absorption spectrum: Scheibe, *Ber.* **59**, 2625 (1926). Soly in glycerol, *see* McEwen, *J. Chem. Soc.* **123**, 2285 (1923). Toxicity studies: J. M. Taylor *et al., Toxicol. Appl. Pharmacol.* **6**, 378 (1964).

Liquid. Agreeable aromatic odor. d_4^{25} 0.9956; d_4^{15} 0.9701, mp −37.3°, bp_{760} 155.5°; bp_{100} 93.0°; bp_{40} 70.7°; bp_{20} 55.8°; bp_{10} 42.2°; bp_5 30.0°; $bp_{1.5}$ 5.4°. n_D^{20} 1.51791. Sol in alcohol and ether. Insol in water. LD_{50} orally in rats: 3700 mg/kg (Taylor).

USE: In perfumery, in organic syntheses.

708. Anisomycin. *1,4,5-Trideoxy-1,4-imino-5-(4-methoxyphenyl)-D-xylo-pentitol 3-acetate; [2R-(2α,3α,4β)]-3-[(4-methoxyphenyl)methyl]-3,4-pyrrolidinediol 3-acetate;* 2-*p*-methoxyphenylmethyl-3-acetoxy-4-hydroxypyrrolidine; Flagecidin. $C_{14}H_{19}NO_4$; mol wt 265.31. C 63.38%, H 7.22%, N 5.28%, O 24.12%. Protein synthesis inhibiting antibiotic isolated from *Streptomyces griseolus* and *S. roseochromogenes*: Sobin, Tanner, Jr., *J. Am. Chem. Soc.* **76**, 4053 (1954); Tanner *et al.*, U.S. pat. **2,691,618** (1954 to Pfizer). Activity: J. E. Lynch *et al., Antibiot. & Chemother.* **4**, 844, 899 (1954). Structure and stereochemistry: Berreboom *et al., J. Org. Chem.* **30**, 2334 (1965); Schaefer, Wheatley, *ibid.* **33**, 166 (1968); Butler, *ibid.* 2136. Biosynthesis: Butler, *ibid.* **31**, 317 (1966). Total synthesis: Oida, Ohki, *Chem. Pharm. Bull.* **16**, 2086 (1968); *ibid.* **17**, 1405 (1969); Felner, Schenker, *Helv. Chim. Acta* **53**, 754 (1970). Chiral synthesis: J. P. H. Verheyden *et al., Pure Appl. Chem.* **50**, 1363 (1978). Stereospecific total synthesis: D. P. Schumacher, S. S. Hall, *J. Am. Chem. Soc.* **104**, 6076 (1982). Mechanism of action: A. Jiménez, D. Vázquez in *Antibiotics* **vol. 5**(pt. 2), F. E. Hahn, Ed. (Springer-Verlag, New York, 1979) pp 1-19. Solubility and stability data: *Antibiot. Ann.* **1954-55**, pp 809-810. Prepn of deacetylanisomycin from anisomycin: Nickell *et al.*, U.S. pat. **2,935,444** (1960 to Pfizer).



Long needles from ethyl acetate or water, mp 140-141°. $[\alpha]_D^{23}$ −30° (methanol). uv max: 224, 277, 283 nm (ε 10800, 1800, 1600). Base is moderately sol in water; sol in lower alcohols, esters, ketones, chloroform; slightly sol in benzene, toluene and hexane. Aq solns are stable over a wide pH range at room temp.

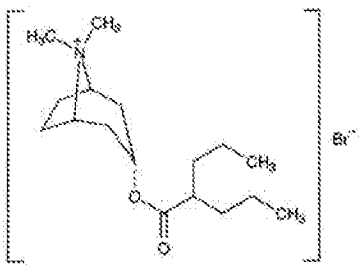
Hydrochloride, $C_{14}H_{19}NO_4.HCl$, crystals from ethyl acetate + ethanol, mp 187-188°. Very sol in water.

Deacetylanisomycin, $C_{12}H_{17}NO_3$, mp 176-179°. $[\alpha]_D^{25}$ −20.0° (methanol), pK 9.2.

USE: Anisomycin and deacetylanisomycin in the eradication of bean mildew, to inhibit other pathogenic fungi in plants.

THERAP CAT: Antiprotozoal (Trichomonas).

709. Anisotropine Methylbromide. *endo-8,8-Dimethyl-3-[(1-oxo-2-propylpentyl)oxy]-8-azoniabicyclo[3.2.1]octane bromide; 3α-hydroxy-8-methyl-1α*H*,5α*H*-tropinium bromide 2-propylvalerate;* 8-methyltropinium bromide 2-propylvalerate; 8-methyl-3-(2-propylpentanoyloxy)tropinium bromide; octatropine methylbromide; Lytispasm; Valpin. $C_{21}H_{38}BrNO_2$; mol wt 362.35. C 56.35%, H 8.90%, Br 22.05%, N 3.87%, O 8.83%. Prepn: Weiner, Gordon, U.S. pat. **2,962,499** (1960 to Endo Labs.). Metabolism: Shindo *et al., Chem. Pharm. Bull.* **19**, 513 (1971).



Crystals from acetone, mp 329°.

Methyl chloride, $C_{17}H_{32}ClNO_2$, crystals from acetone, mp 289°.

THERAP CAT: Anticholinergic.

710. *o*-(*p*-Anisoyl)benzoic Acid. *2-(4-Methoxybenzoyl)benzoic acid;* S-23/46. $C_{15}H_{12}O_4$; mol wt 256.26. C 70.31%, H 4.72%, O 24.97%. Prepn from phthalic anhydride and anisole: Meyer, Turnau, *Monatsh.* **30**, 486 (1909). Alternate route: Arens, Marks, *J. Chem. Soc.* **1956**, 1627.